IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent application of:
FAOUR, J. et al.

Serial No.: 09/770,901
Filed: January 26, 2001

Group Art Unit: 1617
Examiner: Shaojia A. Jiang

For: Pharmaceutical compositions containing A COX-II inhibitor and a muscle relaxant

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on September 17, 2002.

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Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

RESPONSE

In response to the Office Action mailed April 9, 2002, and further to the Notice of Appeal filed September 5, 2002, and the Request for Continued Examination filed herewith, Applicants hereby submit the following response.

REMARKS

Claims 1-8, 10-38 and 40-54 remain pending herein. All claims remain the same. No new claims have been added. No claims have been amended. Reconsideration of the claims as pending is respectfully requested.

Claims 7-8, 12, 16-18, 28-29, 31-37, and 40-48 stand rejected under 37 C.F.R. §112, 2nd para. as being indefinite for the reasons stated in the Office Action mailed September 28, 2001. Insofar as it may apply to the present claims, the rejection is respectfully traversed.

Claim 12 stands objected for use of the terms "slow or rapid release". Claim 18 stands rejected for use of the term "rapidly". Claim 29 stands rejected use of the terms "rapid", "immediate", "slow", and "delayed" release. Claims 31-37 stand rejected for use of the term "delayed but rapid". Applicants submit that these terms are not indefinite as used in the pharmaceutical industry. These terms are widely used in the pharmaceutical industry to definitely and clearly differentiate the various release profiles that dosage forms provide. These

terms concern either the rate at which or the manner in which drug is released from a dosage form or composition. Applicants note that hundreds of issued US patents include these very terms in their respective claims. As evidence thereof, Applicants submit Attachments A-D, which are taken from well-recognized pharmaceutical texts. The terms "rapid", "immediate", "slow", and "delayed" release are defined in the texts. Accordingly, these terms have acquired a definite meaning in the art of the pharmaceutical sciences. Moreover, the specification provides exemplary formulations for each of these different types of release profiles.

A delayed release dosage form is one that exhibits an initial delay in the release of drug after exposure to an environment of use. The period of delay is generally anywhere from minutes to hours.

An immediate release dosage form is one that begins to release drug shortly, generally seconds to minutes, after exposure to an environment of use and therefore does not exhibit a significant delay in release of drug.

A slow release dosage form is one that provides a slow rate of release of drug so that drug is released over a period of hours to days.

A rapid release dosage form is one that releases drug over a period of minutes to 1-2 hours once release has begun. In other words, a rapid release can begin immediately after administration of the dosage form or after a delay period (a lag time) after administration of the dosage form. Accordingly, a delayed but rapid release dosage form is one that delays release of a drug for a lag time after which a rapid release of the drug occurs. In other words, the rapid release of drug is delayed by a period of time.

Applicants submit that the terms "rapid", "immediate", "slow", "delayed" and "delayed but rapid" are well defined and understood by the artisan of ordinary skill. Applicants also submit that the use of these terms in the claims does not render the claims indefinite since these terms are widely used in the pharmaceutical industry and their definitions are well known by the artisan of ordinary skill.

Claims 7-8, 16-17 and 40-48 contain the terms SC-5766, SC-58215 and T-614. These terms are not trademarks. Rather, they are drug development candidate terms, i.e., they are terms used by the pharmaceutical industry to identify promising drug candidates that are in the development stage. For example, when a drug's is structure is known by a company but it has not yet been assigned a tradename, then the drug is identified by its development candidate

number. The letters that form part of the number identify the pharmaceutical company to which the drug candidate is associated. Applicants note that the term "SC-58215" is a typographical error that should read "SC-58125". Also, the term "SC-5766" is a typographical error that should read "SC-57666". Moreover, the drug development candidate SC-57666 is synonymous with SC-58125. The drug development candidate T-614 is actually named [N-(3-formylamino-4-oxo-6-phenoxy-4H-chromen-7-yl)methanesulfonamide] or (3-formylamino-7-methylsulfonyl-amino-6-phenoxy-4H-1-benzopyran-4-one). The drug development candidate SC-57666 (SC-58125) is actually 1-fluoro-4-(2-(4-(methylsulfonyl)phenyl)-1- cyclopenten-1-yl)-benzene. In order to provide further clarification, Applicants have also provided the complete chemical names of NS-398 (N-(2-cyclohexyloxy-4-nitrophenyl) methanesulfonamide) and DUP-697 (5-bromo-2-(4-fluorophenyl)-3-(4-methylsulfonyl) thiophene).

Applicants have amended the specification (page 3, lines 5-11; page 7, lines 22-27) and claims (8, 17, and 40) to identify the drugs by their chemical names. Applicants submit that no new matter has been added. A Marked-up Version of the Specification, Clean Version of the Specification, Marked-Up Version of the Claims, and Clean Version of the Claims are enclosed herewith. Entry of the amendments indicated thereon into the record is requested. Applicants request replacement of current pages 3, 7, 44, 45 and 47 with substitute pages 3, 7, 44, 45 and 47 enclosed herewith.

Accordingly, Applicants respectfully submit that the rejection of claims 7-8, 12, 16-18, 28-29, 31-37, and 40-48 under 37 C.F.R. §112, 2nd para. has been overcome and request that it be withdrawn.

Claims 1-8, 10-38, and 40-54 stand rejected under 37 C.F.R. §103(a) as being unpatentable over Burch et al. Examiner states that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a COX-II inhibitor, such as rofecoxib, in combination with a muscle relaxant, such as pridinol, in a pharmaceutical composition or dosage. Examiner also states that individual use of COX-II inhibitors and muscle relaxants for the treatment of pain is known and that the combined use of pridinol with other analgesics for the treatment of pain is known. Examiner states that it is considered *prima facie* obvious to combine these components into a composition for the treatment of pain and "at least additive therapeutic effects would have been reasonably expected." Finally, Examiner states that the declaration of Dr. Ethel C. Feleder (mailed December 20, 2001) is insufficient to establish the

fact that the claimed combination has any unexpected synergism since the declaration lacks any factual evidence for the synergism produced by the instant invention, and the record contains no clear and convincing evidence of unexpected results or unexpected synergistic analgesic effect produced by the claimed combination over the prior art. Insofar as it may apply to the present claims, this rejection is respectfully traversed.

Submitted herewith is a Supplemental Declaration Under Rule 37 C.F.R.§1.132 by Dr. Feleder. The declaration includes the results of a side-by-side comparison between a formulation according to the present invention and a formulation of the closest prior art. As stated in the declaration, a formulation comprising an NSAID (diclofenac) and a muscle relaxant (pridinol) is commercially available from Bristol-Myers Squibb in Argentina under the trademarks VOLTRAN FLEX® and VESALION FLEX®. A side-by-side comparison on an equi-dose basis was conducted between two parenteral formulations: a first containing diclofenac and pridinol and a second containing rofecoxib and pridinol. A Writhing Test, which is well known in the art as a test for determining the analgesic efficacy of a drug or a combination of drugs, was used to evaluate the differences between the formulations. The method, formulations and results are detailed in the declaration.

In brief, when each drug was administered individually at sub-therapeutic doses, none of the drugs provided a statistically significant improvement over control in reducing the number of observed contortions in mice. When diclofenac and pridinol, each present in a sub-therapeutic dose, were administered in combination, a statistically significant improvement over control in reducing the number of contortions in mice WAS NOT observed. This means that no synergy was observed for the combination of diclofenac and pridinol. However, when rofecoxib and pridinol, each present in a sub-therapeutic dose, were administered in combination, a statistically significant improvement over control in reducing the number of contortions in mice WAS observed.

The data demonstrate that the combination of rofecoxib (a COX-II inhibitor) and pridinol (a muscle relaxant) unexpectedly provides an improvement over the closest prior art. Moreover, unlike the prior art, the claimed combination can provide a synergistic analgesic effect, since both drugs, when administered individually at sub-therapeutic doses, did not provide an observed analgesic effect in the writhing test.

In the first declaration of Dr. Feleder, Applicants cited examples of combinations of analgesic agents that did not provide at least an additive analgesic effect as suggested by Examiner. This in itself is sufficient to establish the non-obviousness of the claimed invention, which demonstrates an improvement over a formulation of the closest prior art. However, Applicants submit that even IF the artisan of ordinary skill were to expect at least an additive analgesic effect upon the combined administration of a COX-II inhibitor and a muscle relaxant, the artisan of ordinary skill would not expect the synergistic analgesic effect that the present inventors have discovered.

Accordingly, the claimed combination is not *prima facie* obvious and is therefore patentable over the art of record. In view of the above, applicants submit that the rejection of claims 1-8, 10-38 and 40-54 under 37 C.F.R.§103(a) has been overcome and request that it be withdrawn.

Pending allowance of claims 1-8, 10-38 and 40-54, Applicants request reconsideration of the subject matter of claims 9 and 39, inasmuch as claims 9 and 39 include the subject matter of the claims from which they depend.

Applicants respectfully request entry of this Response into the record and full consideration thereof.

In view of all the foregoing, Applicants respectfully submit that the claims are patentable over the art of record and in form for allowance. An early notice of allowance thereof is requested.

Respectfully submitted,

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Pharmaceutical Dissolution Testing

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course of the drug concentration in the blood. These dosage forms add an extra dimension to the traditional functions of the dosage form, being a mere carrier for drug storage, portability, and administration. It is apparent that any dosage form other than conventional, be it prolonged-release, sustained-release, controlled-release, or others, involves some sort of modification in the release characteristics of the drug incorporated within it.

Compendia describe *modified-release dosage forms* as those forms for which the drug release characteristics as a function of time and/or conditions at the site of dissolution are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or compressed tablets and capsules. Currently, *Pharmacopoeial Forum* proposes two modified-release dosage forms.

Delayed-release dosage forms are defined as those that release a drug (or drugs) at any time other than promptly after administration (e.g., enteric-coated products). The USP limit for enteric-coated tablets requires that the tablets survive a 1-h acid treatment in the disintegration apparatus without disks. On successful passing of this step, they must show 75% dissolution in 45 min in pH 6.8 buffer.

Extended-release dosage forms are defined as those that allow at least a twofold reduction in frequent dosing compared to the drug presented in a conventional form (e.g., a solution or fast-releasing conventional solid dosage form). These dosage forms are popularly known as *timed-release, sustained-release*, or *prolonged-release dosage forms*.

Like any other solid dosage form, the rate of drug release from modified-release solid dosage forms depends on the rate of dissolution. In the case of solutions, it depends on the rate of diffusion. Present technology utilizes either of these possibilities alone or in combination. On the basis of the Noyes–Whitney equation describing the dissolution process and Fick's law of diffusion, Huttenrauch (1) defined the principles of modified-release dosage forms depicted in Table 8.1. Depending on the dosage form, the dissolution rate can be further modified by excipients, formulation, and technology of production.

The mechanism of release of the drugs from various modified-release dosage forms is different for each form. Additionally, it has long been recognized that these dosage forms are not only drug products but also devices and therefore "no single in vitro test will completely reflect the availability of the drug" (2). The usual tests of disintegration time found in pharmacopoeias do not apply to oral modified-release dosage forms, since the release rate per unit time is the critical factor (3).

Without entering into questionable and conflicting controversies regarding the tru validity of these dosage forms as to their being either, prolonged-, sustained, or controlled-release characteristics, in this chapter we focus n the

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blood level may result. For example, drugs with short half-lives require frequent dosings to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multipl - dosing can produce the desired drug blood level for extended periods of time. Frequently, howev r, these problems are significant nough to make drug therapy with conventional dosage forms less desirable than sustained-release drug therapy. This fact, coupled with th intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of sustained-release drug delivery systems. There are numerous potential advantages of sustained-release drug therapy that will be discussed in the next section.

Sustained-Release Drug Therapy

As already mentioned, conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments, and suppositories. For purposes of this discussion, these dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme:

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Absorption Pool} \xrightarrow[\text{absorption}]{k_a} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

The absorption pool represents a solution of the drug at the site of absorption, and the terms k_r, k_a, and k_e are first-order rate constants for drug release, absorption, and overall elimination, respectively. Immediate release from a conventional dosage form implies that $k_r \ggg k_a$ or, alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate-limiting step in delivery of the drug to its target area. For nonimmediate release dosage f rms, $k_r \lll k_a$, that is, release of drug from the dosage form is the rate limiting step. This causes the above kinetic scheme to reduce to the following:

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

Essentially, the absorptive phase of the kinetic scheme becomes insignificant compared to the drug release phase. Thus, the effort to develop a nonimmediate release delivery system must be primarily directed at altering the release rate by affecting the value of k_r. The many ways in which this has been attempted will be discussed later in this chapter.

Nonimmediate release delivery systems may be conveniently divided into four categories:

1. Delayed release
2. Sustained release
   a. controlled release
   b. prolonged release
3. Site-specific release
4. Receptor release

Delayed-release systems are those that utilize repetitive, intermittent dosings of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed-release systems include repeat action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating. A delayed-release dosage form does not produce r maintain uniform drug blood levels within the therapeutic range, as shown in Fig 92-3, but nonetheless is more effective for patient compliance than conventi nal dosage forms.

Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful at maintaining c nstant drug levels in the blood r target tissue, it is considered a

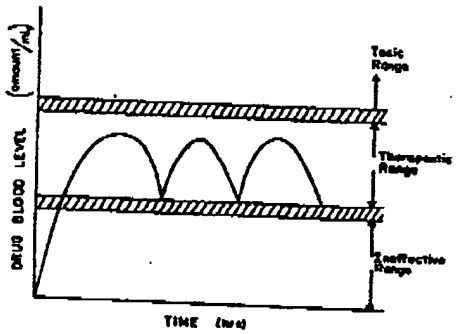

Fig 92-3. Typical drug blood level versus time profiles for delayed release drug delivery by a repeat-action dosage form.

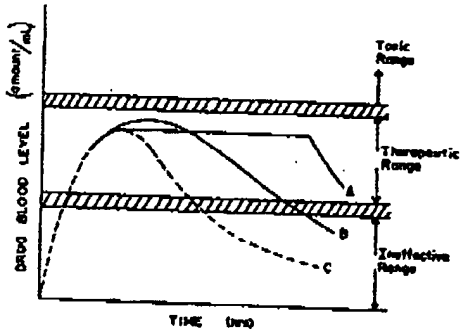

Fig 92-4. Drug blood level versus time profiles showing the relationship between controlled release (A), prolonged release (B), and conventional release (C) drug delivery.

controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a *prolonged-release* system. This is illustrated in Fig 92-4.

Site-specific and *receptor release* refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is a certain organ or tissue; for receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery.

Release Rate and Dos C nsider ti ns

Although it is not necessary or desirable to maintain a constant level of drug in th blood or target tissu for all therapeutic cases, this is the ideal goal of a sustained-release deliv ry system. In fact, in some cases optimum therapy is achieved by oscillating, rather than constant, drug levels. An example of this would be antibiotic therapy, where the activity of the drug is required only during growth phases of the microorganism. A constant drug level will succeed at curing

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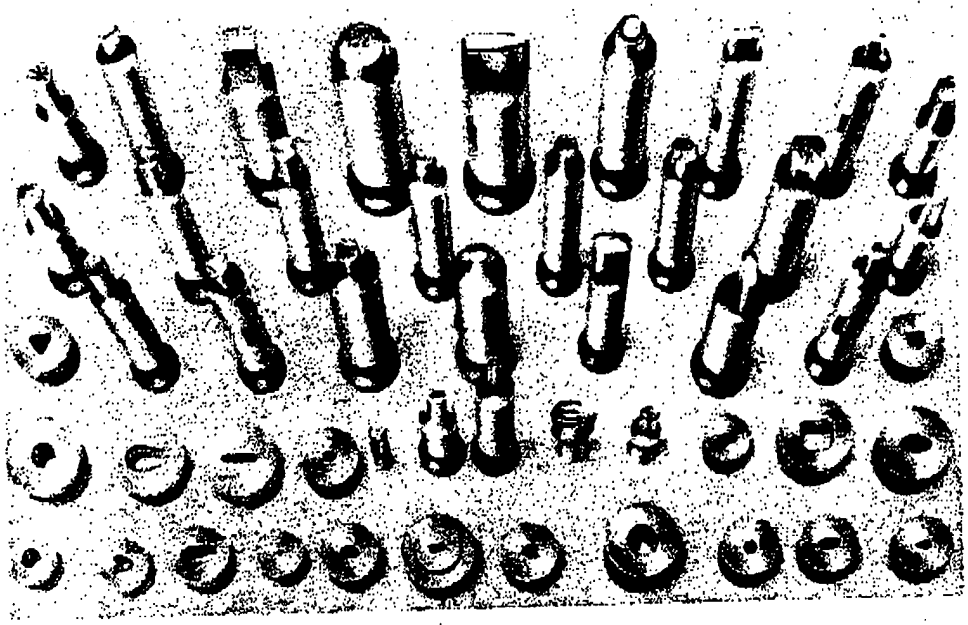

Fig. 7.23 *Various Stokes punches and dies for the production of distinctive tablets. (Courtesy of Stokes Equipment Division, Pennwalt Chemicals Corporation.)*

ing. It serves the purpose of protecting the enclosed drug from the environment and provides a barrier to objectional tasting or smelling drugs. The sugar coating also enhances the appearance of the compressed tablet and permits the imprinting of identifying manufacturer's information. Among the disadvantages to sugar-coating tablets are the time and expertise required in the coating process and the increase in the size, weight, and shipping costs of the tablets. Sugar-coated tablets may be 50% larger and heavier than the original uncoated tablets.

Film-Coated Tablets (F.C.T.)

Film-coated tablets are compressed tablets coated with a thin layer of a polymer capable of forming a skin-like film over the tablet. The film is usually colored and has the advantage over sugar-coatings in that it is more durable, less bulky, and less time-consuming to apply. By its composition, the coating is designed to rupture and expose the core tablet at the desired location within the gastrointestinal tract.

Gelatin-Coated Tablets

A recent innovation in tablet coating is the gelatin-coated tablet. The innovator product, termed GELCAPS, is a capsule-shaped compressed tablet (Fig. 7.25) that allows the coated product to be about one-third smaller than a capsule filled with an equivalent amount of powder. The gelatin coating facilitates swallowing and compared to unsealed capsules, gelatin-coated tablets are more tamper-evident.

Enteric-Coated Tablets (E.C.T.)

Enteric-coated tablets have delayed-release features. They are designed to pass unchanged through

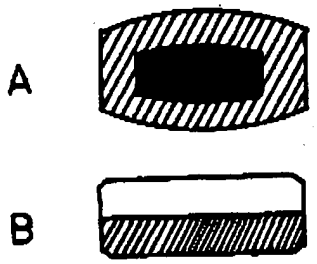

Fig. 7.24 *Diagram of multiple-compressed tablets. A, having a core of one drug and a shell of another, and B, a multiple-layered tablet of two drugs.*

Fig. 7.25 *Cut-away view of "Gelcaps" dosage form. A gelatin-coated capsule-shaped tablet. Dosage form is more easily swallowed than a comparable tablet, smaller than an equivalent capsule, and tamper-evident. (Courtesy of McNeil Consumer Products Co.)*

the stomach with transit to the intestines where the tablets disintegrate and allow drug dissolution and absorption and/or effect. Enteric coatings are employed in instances in which the drug substance is destroyed by gastric acid, is particularly irritating to the gastric mucosa, or when by-pass of the stomach substantially enhances drug absorption.

Buccal or Sublingual Tablets

Buccal or sublingual tablets are flat, oval tablets intended to be dissolved in the buccal pouch (*buccal tablets*) or beneath the tongue (*sublingual tablets*) for absorption through the oral mucosa. They enable the oral absorption of drugs that are destroyed by the gastric juice and/or are poorly absorbed from the gastrointestinal tract. Buccal tablets are designed to erode slowly, whereas those for sublingual use (as nitroglycerin sublingual tablets) dissolve promptly and provide rapid drug effects. *Lozenges* or *troches*, are disc-shaped, solid dosage forms containing a medicinal agent and generally a flavoring substance in a hard candy or sugar base. They are intended to be slowly dissolved in the oral cavity usually for localized effects although some may be formulated for systemic absorption.

Chewable Tablets

Chewable tablets, which have a smooth, rapid disintegration when chewed or allowed to dissolve in the mouth, have a creamy base usually of specially flavored and colored mannitol. Chewable tablets are especially useful for the administration of tablets of large-size to children and adults who have difficulty swallowing solid dosage forms.

Effervescent Tablets

Effervescent tablets are prepared by compressing granular effervescent salts that release gas when in contact with water. These tablets generally contain medicinal substances which dissolve rapidly when added to water.

Molded Tablets (M.T.)

Certain tablets, as tablet triturates, may be prepared by molding rather than by compression. The resultant tablets are very soft, soluble, and are designed for rapid dissolution.

Tablet Triturates (T.T.)

Tablet triturates are small, usually cylindrical, molded (M.T.T.) or compressed tablets (C.T.T.) containing small amounts of usually potent drugs. Today only a few tablet triturate products are available commercially, with most of these produced by tablet compression. Since tablet triturates must be readily and completely soluble in water only a minimal amount of pressure is applied during their manufacture. A combination of sucrose and lactose is usually the diluent. The few tablet triturates which remain are used sublingually, as nitroglycerin tablets.

In the past, pharmacists employed tablet triturates in compounding procedures. For example, they were inserted into capsules or dissolved in liquid preparations to provide accurate amounts of potent drug substances.

Hypodermic Tablets (H.T.)

Hypodermic tablets are no longer available in the United States. They were originally used by physicians in the extemporaneous preparation of parenteral solutions. The required number of tablets was dissolved in a suitable vehicle, sterility attained, and the injection performed. The tablets were a convenience, since they could be easily carried in the physician's medicine bag and injections prepared to meet the needs of the individual patients. However, the difficulty in achieving sterility, the current availability of prefabricated injectable products, some in disposable syringes, have eliminated the need for hypodermic tablets.

Dispensing Tablets (D.T.)

Dispensing tablets are no longer in use. They might better have been termed *compounding tablets* because they were used by the pharmacist in compounding prescriptions and were *not* dispensed as such to the patient. The tablets contained large amounts of highly potent drug substances enabling the pharmacist to rapidly obtain premeasured amounts for compounding multiple dosage units. These tablets had the dangerous potential of being inadvertently dispensed as such to patients.

Fig. 7.26 Packages of a drug product of two different tablet strengths, with one scored for ease of breaking in half. (Courtesy of Marion Laboratories.)

Immediate Release Tablets (I.R.)

Immediate release tablets are designed to disintegrate and release their medication absent of any special rate-controlling features as special coatings and other techniques.

Instant Disintegrating / Dissolving Tablets

Instant-release tablets are characterized by disintegrating/dissolving in the mouth within one minute; some within 10 seconds [e.g., Claritin Reditabs (loratadine), Schering]. Tablets of this type are designed for pediatric and geriatric patients or for any patient who has difficulty in swallowing tablets. After placing them on the tongue they liquefy and the patient swallows the liquid. A number of techniques are used to prepare these tablets involving lyophilization (e.g., Zydis, R.P. Scherer), soft direct compression (e.g., WOW-Tab, Yamanouchi-Shaklee Pharma), and other methods (e.g., Quicksolv, Janssen). These tablets are prepared using very water-soluble excipients designed to "wick" water into the tablet for rapid disintegration/dissolution. They have the stability characteristics of other solid dosage forms.

Extended Release Tablets (E.R.)

Extended-release tablets (sometimes called "controlled release (CR)" tablets) are designed to release their medication in a predetermined manner over an extended period of time. They are discussed in Chapter 8.

Vaginal Tablets

Vaginal tablets, also called *vaginal inserts*, are uncoated and bullet- or ovoid-shaped tablets which are inserted into the vagina for localized effects. They are prepared by compression and shaped to fit snugly on plastic inserter devices which accompany the product. They contain antibacterials for the treatment of vaginitis caused by *Hemophilus vaginalis* or antifungals for the treatment of vulvovaginitis candidiasis caused by *Candida albicans* and related species.

Compressed Tablets

The physical features of compressed tablets are well known. Some are: round, oblong, or unique in shape; thick or thin; large or small in diameter; flat or convex; unscored or *scored* (Fig. 7.26) in halves, thirds, or quadrants; engraved or imprinted with an identifying symbol and/or code number; coated or uncoated; colored or uncolored; single layer, or bi- or tri-layered.

Tablet diameters and shapes are determined by the die and punches used in the compression of the tablet. The less concave the punches, the more flat the resulting tablets; conversely, the more concave the punches, the more convex the resulting tablets (Fig. 7.27). Punches having raised impressions will produce recessed impressions on the tablets; punches having recessed etchings will produce tablets having raised impression or monograms. Monograms may be placed on one or on both sides of a tablet, depending upon whether monogram-producing lower and/or upper punches are used.

Quality Standards and Compendial Requirements

In addition to the apparent features of tablets, pharmacists are aware that tablets must meet other physical specifications and quality standards. These include criteria for tablet weight, weight variation,

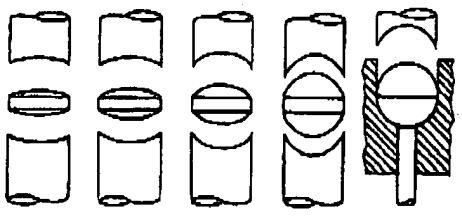

Fig. 7.27 Contours of the punches determine the shape of the tablets. From left to right, flat face, shallow cup, standard cup, deep cup, and modified ball. (Courtesy of Cherry-Burrell Corporation.)

Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2000
BP

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GUIDANCE FOR INDUSTRY[1]

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

I. INTRODUCTION

This guidance provides recommendations for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications who wish to request a waiver of in vivo bioavailability (BA) and/or bioequivalence (BE) studies for immediate release (IR) solid oral dosage forms. These waivers are intended to apply to (1) subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR dosage forms during the IND period, and (2) in vivo BE studies of IR dosage forms in ANDAs. Regulations at 21 CFR part 320 address the requirements for bioavailability (BA) and BE data for approval of drug applications and supplemental applications. Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR 320.22. This guidance explains when biowaivers can be requested for IR solid oral dosage forms based on an approach termed the Biopharmaceutics Classification System (BCS).

II. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability.[2] According to the BCS, drug substances are classified as follows:

Class 1:	High Solubility – High Permeability
Class 2:	Low Solubility – High Permeability
Class 3:	High Solubility – Low Permeability

[1] This guidance has been prepared by the Biopharmaceutics Classification System Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] Amidon, G. L., H. Lennernäs, V. P. Shah, and J. R. Crison, "A Theoretical Basis For a Biopharmaceutics Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability," *Pharmaceutical Research*, 12: 413-420 (1995).

Class 4: Low Solubility – Low Permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo.[2] However, when the in vivo dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of in vivo BA or BE may not be necessary for drug products containing Class 1 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods (21 CFR 320.22(e)). The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

C. Dissolution

In this guidance, an IR drug product is considered *rapidly dissolving* when no less than 85% of the labeled amount of the drug substance dissolves within 30

minutes, using *U.S. Pharmacopeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

III. METHODOLOGY FOR CLASSIFYING A DRUG SUBSTANCE AND FOR DETERMINING THE DISSOLUTION CHARACTERISTICS OF A DRUG PRODUCT

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS:

A. Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at 37 ± 1°C in aqueous media with a pH in the range of 1-7.5. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. For example, when the pKa of a drug is in the range of 3-5, solubility should be determined at pH = pKa, pH = pKa +1, pH = pKa-1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.[3] If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported along with other stability data recommended in section III.B.3.

The solubility class should be determined by calculating the volume of an aqueous medium sufficient to dissolve the highest dose strength in the pH range of 1-7.5. A drug substance should be classified as highly soluble when the highest dose strength is soluble in ≤ 250 ml of aqueous media over the pH range of 1-7.5.

[3] See the FDA guidance for industry on *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987), posted at http://www.fda.gov/guidance/index.htm.

#19
10/09/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent application of: §
FAOUR, J. et al. §
§
Serial No.: 09/770,901 § Group Art Unit: 1617
Filed: January 26, 2001 § Examiner: Shaojia A. Jiang

For: Pharmaceutical compositions containing A COX-II inhibitor and a muscle relaxant

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on 9/19/02.

Rick Matos
Typed or printed name of person mailing paper

Signature of person mailing paper

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

SUPPLEMENTAL DECLARATION UNDER RULE 37 C.F.R.§1.132

Further to the Office Action mailed April 9, 2002, the Declaration mailed January 2, 2002, the undersigned hereby declares as follows:

My name is Ethel C. Feleder. I reside in Luis Maria Campos 449, 2° A, Buenos Aires, Argentina.

I am knowledgeable in the area of Pharmaceutical Sciences and in particular in the area of the clinical evaluation of pharmaceutical formulations. My education, experience, publications and awards are summarized in my curriculum vitae, which is attached.

I am familiar with the subject matter of the invention disclosed and claimed in the above-identified patent application. In particular, I am familiar with conventional methods of analgesic therapy with individual drugs and with combinations of drugs.

With regard to the subject matter of claims 1-8, 40-45 and 49-54, I understand that the claims cover a pharmaceutical composition comprising a COX-II inhibitor and a muscle relaxant.

With regard to the subject matter of claims 10-38 and 46-48, I understand that the claims cover a pharmaceutical dosage form comprising a COX-II inhibitor and a muscle relaxant.

As a medical doctor, it is my belief that the claimed pharmaceutical compositions and dosage forms provide significant advantages over conventional analgesic compositions and dosage

forms used in pain therapy. In particular, the claimed pharmaceutical composition and dosage form provide an enhanced analgesic affect as compared to the administration of either agent alone and as compared to the administration of an NSAID and a muscle relaxant. The exemplary formulation of rofecoxib and pridinol, the claimed composition and the claimed dosage form provide an unexpectedly improved analgesic effect over an equidose composition comprising diclofenac (an NSAID) and pridinol.

A number of prior art references, submitted under cover of the Supplemental Information Disclosure Statement mailed herewith, disclose the coadministration of an NSAID and a muscle relaxant. Commercial products sold under the name Voltaren Flex® by Novartis or Vesalion Flex® by Bristol M.S. in Argentina contains diclofenac and pridinol

A side-by-side study to compare the analgesic effects of the claimed composition versus a prior art composition was conducted. A writhing test was conducted according to the method previously described by Siegmund E et al. (*Proc Soc Exp Biol Med* 95: 729-731, 1957) with minor modifications. The method is well known in the art as a test for determining the analgesic effect of a drug or combination of drugs. The intraperitoneal administration of an irritating agent provokes a very stereotypical behavior in the mouse and the rat, which is characterized by abdominal contractions, movements of the body as a whole, twisting of dorsoabdominal muscles, and a reduction in motor activity and motor incoordination. A positive result in the Writhing Test is generally predictive of human efficacy, since there is a good correlation between analgesic activity and sensitivity (ED50) in mice with human analgesic effects. A negative result is not necessarily predictive of lack of human efficacy, since a negative result can be obtained by using subtherapeutic drug doses. The use of subtherapeutic doses in this test is particularly useful in helping to identify synergistic drug combinations. A positive result is obtained when a drug or drug combination reduces the total number of contortions (writhes) when compared to a control in a statistically significant manner. The Writhing Test is also used when comparing the relative analgesic effect of a first drug to another drug or a first drug combination to another drug combination. The study was conducted as follows.

12 hour fasting mice weighing aproximately 30 g were divided into different groups in a number of 12 per group. Each group received an intraperitoneal dose of rofecoxib, diclofenac or a combination of rofecoxib plus pridinol or diclofenac plus pridinol, as follows: The first group was administered rofecoxib (16 mg / kg of body weight). The second group was administered

rofecoxib (16 mg / kg of body weight) in combination with pridinol (0.64 mg / kg of body weight). The third group was administered diclofenac (16 mg / kg of body weight). The fourth group was administered diclofenac (16 mg / kg of body weight) in combination with pridinol (0.64 mg / kg of body weight). Other groups of mice, who received the vehicle of either rofecoxib or pridinol, were considered as control of each experimental group. The diclofenac-containing clear solutions were administered in an aqueous vehicle in physiological salt. The rofecoxib-containing clear solutions were administered in an aqueous vehicle containing carboxymethylcellulose in order to help dissolve the rofecoxib. 30 minutes after the injection of the investigational drugs, the mice were administered an acetic acid–containing solution by intraperitoneal injection. Then, the number of contortions for each mouse was counted during a period of 10 min.

Separate studies were conducted to confirm that active drugs or vehicle compositions had no effect on writhe production in mice. The tests were also performed on different groups of mice at doses of 32 mg analgesic agent (diclofenac or rofecoxib) / kg body weight and again with 64 mg analgesic agent / kg body weight. The dose of pridinol was kept constant. Since each particular group of mice has a different response to the acetic acid-containing solution, the responses were normalized across the groups. The following results were obtained.

1. When administered alone and at the above-noted doses, neither diclofenac nor rofecoxib nor pridinol provided a statistically significant reduction in the number of contortions observed as compared to control. This means that the drugs were dosed at subtherapeutic levels, considering that both drugs have been reported to produce analgesic effects in different animal models.
2. When diclofenac was administered in combination with pridinol, no statistically significant reduction in the number of contortions was observed as compared to control. This means that pridinol did not enhance (either additively or synergistically) the analgesic efficacy of diclofenac at the doses tested.
3. When rofecoxib was administered in combination with pridinol, a statistically significant reduction in the number of contortions was observed as compared to control. This means that pridinol synergistically enhanced the analgesic efficacy of rofecoxib at the doses tested, since each agent alone did not provide an analgesic effect at the doses tested.

Therefore, it is truly unexpected that the combined administration of a COX-II inhibitor and a muscle relaxant provides an improved, additive or synergistic analgesic effect when administered to a subject as compared to the analgesic effect provided by the administration of either agent alone or as compared to the administration of an NSAID and a muscle relaxant.

I further declare that the statements made herein, to my knowledge, are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 09/09/2002

Dr. Ethel C. Feleder, M.D., Ph.D.

(N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide)

release of each of the COX-II inhibitor and the muscle relaxant; 5) the pharmaceutical composition provides therapeutically effective plasma levels of the COX-II inhibitor and muscle relaxant for a period of at least 12 hours after administration; and/or 6) the COX-II inhibitor is selected from the group consisting of rofecoxib (VIOXX™, MK-0966), celecoxib (CELEBREX™, SC-58635), flosulide (CGP-28238), NS-398, DUP-697, (5-bromo-2-(4-fluorophenyl)-3-(4-methylsulfonyl)thiophene) meloxicam, 6-methoxy-2-naphthylacetic acid (6-MNA), nabumetone (prodrug for 6-MNA), etodolac, nimesulide, ~~SC-5766, SC-58215,~~ SC-57666, SC-58125; 1-fluoro-4-(2-(4-(methylsulfonyl)phenyl)-1-cyclopenten-1-yl)-benzene), T-614, and combinations thereof. (N-(3-formylamino-4-oxo-6-phenoxy-4H-chromen-7-yl) methane sulfonamide)

Another aspect of the invention provides a controlled release combination device comprising:

a core comprising a therapeutically effective amount of a COX-II inhibitor and at least one osmotic agent or osmopolymer, wherein the core provides a controlled release of the COX-II inhibitor;

a semipermeable membrane surrounding the core and having a passageway there through; and

an external coat comprising a therapeutically effective amount of a muscle relaxant, wherein the external coat provides a rapid release of the muscle relaxant; and wherein:

at least 75% of the COX-II inhibitor is released within 24 hours, and at least 75 % of the muscle relaxant is released within 40 minutes after exposure of the osmotic device to an aqueous solution.

In other embodiments, the external coat is applied by spray coating rather than by compression coating. By spray coating rather than compression coating the external coat is thinner, and therefore a smaller osmotic device is formed.

Other embodiments include those wherein: 1) the controlled release device further comprises an inert and erodible water soluble lamina interposed the semipermeable membrane and the drug-containing outer coating; 2) the water soluble lamina comprises poly(vinylpyrrolidone)-(vinyl acetate) copolymer; and/or 3) the controlled release device is an osmotic device.

targeted, enteric or timed-release dosage forms. Suitable dosage forms for this embodiment include, for example, a layered patch, layered or coated tablet, layered or coated osmotic device, capsule containing a mixture of beads that provide different release profiles for the drugs, and layered or coated implant.

Each drug will be released independently according to a rapid, immediate, controlled, sustained, slow, timed, targeted, pseudo-first order, first order, pseudo-zero order, zero-order, second order and/or delayed release profile. The particular release profiles for the COX-II inhibitor and muscle relaxant in a particular dosage form will depend upon the specific COX-II inhibitor and muscle relaxant present. For example, a dosage form might provide: 1) a controlled release of the first drug and a controlled release of the second drug; 2) a controlled release of the second drug and a rapid release of the first drug; 3) a controlled release of the first drug and a rapid release of the second drug; 4) a rapid release of the first drug and the second drug; 5) a rapid release of the first drug and a delayed but rapid release of the second drug; 6) a rapid release of the first drug and a timed but controlled release of the second drug; 7) a rapid release of the second drug and a delayed but rapid release of the first drug, and 8) a rapid release of the second drug and timed but controlled release of the first drug.

COX-II inhibitors useful in the present invention include those compounds that are selective for COX-II receptor inhibition over COX-I receptor inhibition or that are COX-II specific receptor inhibitors. These compounds include, for example, rofecoxib (VIOXX™, MK-0966), celecoxib (CELEBREX™, SC-58635), meloxicam, nimesulide, (N-(2-cyclohexyloxy-4-nitrophenyl) methanesulfonamide) etodolac, flosulide (CGP-28238), NS-398, DUP-697, meloxicam, 6-methoxy-2-naphthylacetic acid (6-MNA), nabumetone (prodrug for 6-MNA), nimesulide, ~~SC-57666~~ ~~SC-58215~~, and ~~T-614~~. Other suitable COX-II inhibitors are disclosed in PCT International Publications No. WO 99/25382, No. WO 94/15932, No. WO 96/03388, No. WO 95/00501, No. WO 95/18799, No. WO 98/50075, No. WO 99/13799 and No. WO 96/08482, the entire disclosures of which are hereby incorporated by reference. Still other suitable COX-II inhibitors are disclosed in Patents No. FR 2747123 or FR 2747124, the entire disclosures of which are hereby incorporated by reference. Additional suitable COX-II inhibitors are disclosed in US Patents No. 5,393,790, No. 5,409,944,

(5-bromo-2-(4-fluorophenyl)-3-(4-methylsulfonyl)-4-thiophene)

SC-57666 (SC-58125; 1-fluoro-4-(2-(4-(methylsulfonyl)phenyl)-1-cyclopenten-1-yl)benzene)

T-614 (N-(3-formylamino-4-oxo-6-phenoxy-4H-chromen-7-yl)methanesulfonamide)

tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide.

8) (Amended) The pharmaceutical composition of claim 1, wherein the COX-II inhibitor is selected from the group consisting of rofecoxib, celecoxib, flosulide, NS-398, DUP-697, meloxicam, 6-methoxy-2-naphthylacetic acid, nabumetone, etodolac, nimesulide, SC-57666, ~~[5766, SC-58215]~~ T-614, and combinations thereof.

10) A pharmaceutical dosage form comprising:

a) a therapeutically effective amount of a COX-II inhibitor;

b) a therapeutically effective amount of a muscle relaxant; and

c) at least one pharmaceutical excipient.

11) The pharmaceutical dosage form of claim 10, wherein the dosage form is selected from the group consisting of a gel, cream, ointment, pill, tablet, capsule, liquid, suspension, osmotic device, bead, granule, spheroid, particulate, paste, prill, reconstitutable solid, powder, and injectible liquid.

12) The pharmaceutical dosage form of claim 10, wherein the dosage form independently provides a controlled, delayed, sustained, immediate, timed, slow or rapid release of each of the COX-II inhibitor and the muscle relaxant when exposed to an aqueous environment.

13) The pharmaceutical dosage form of claim 10, wherein the dosage form provides therapeutically effective plasma levels of the COX-II inhibitor for a period up to at least about 12 hours after administration to a subject.

14) The pharmaceutical dosage form of claim 10, wherein after administration to a subject the dosage form provides therapeutically effective plasma levels of the muscle relaxant for a period of administration sufficient to enhance the therapeutic benefit provided by the COX-II inhibitor.

15) The pharmaceutical dosage form of claim 10, wherein the pharmaceutical dosage form is adapted for oral, buccal, ocular, otic, gastrointestinal, dermal, rectal, vaginal, cervical, intrauterine, epidermal, transdermal, implant, mucosal, parenteral, sublingual, nasal, or pulmonary delivery.

16) The pharmaceutical dosage form of claim 10, wherein the muscle relaxant is selected from the group consisting of alcuronium, alosetron, aminophylline, baclofen, carisoprodol, chlorphenesin, chlorphenesin carbamate, chlorzoxazone, chlormezanone, cyclobenzaprine, dantrolene, decamethonium, diazepam, dyphylline, eperisione, ethaverine, gallamine triethiodide, hexafluorenium, mephenesin, metaxalone, methocarbamol, metocurine iodide, orphenadrine, pancuronium, papaverine, pipecuronium, pridinol, succinylcholine, theophylline, tizanidine, tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide.

17) (Amended) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor is selected from the group consisting of rofecoxib, celecoxib, flosulide, NS-398, DUP-697, meloxicam, 6-methoxy-2-naphthylacetic acid, nabumetone, etodolac, nimesulide, SC-57666, ~~5766, SC-58215~~, T-614, and combinations thereof.

18) The pharmaceutical dosage form of claim 10, wherein each drug is released rapidly and the dosage form provides therapeutically effective levels of each drug for a period of at least 12 hours after administration to a subject.

19) The pharmaceutical dosage form of claim 18, wherein the period is about 12 to 60 hours.

20) The pharmaceutical dosage form of claim 19, wherein the period is about 12 to 30 hours.

21) The pharmaceutical dosage form of claim 19, wherein the period is about 18 to 48 hours.

22) The pharmaceutical dosage form of claim 10, wherein after administration to a subject the plasma level of the COX-II inhibitor or muscle relaxant is dependent upon the plasma level of the muscle relaxant or COX-II inhibitor, respectively.

23) The pharmaceutical dosage form of claim 10, wherein after administration to a subject the plasma level of the COX-II inhibitor or muscle relaxant is independent of the plasma level of the muscle relaxant or COX-II inhibitor, respectively.

34) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the muscle relaxant and a delayed but rapid release of the COX-II inhibitor after exposure to an aqueous environment.

35) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the muscle relaxant and a timed but controlled release of the COX-II inhibitor after exposure to an aqueous environment.

36) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the COX-II inhibitor and a delayed but rapid release of the muscle relaxant after exposure to an aqueous environment.

37) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the COX-II inhibitor and a timed but controlled release of the muscle relaxant after exposure to an aqueous environment.

38) The pharmaceutical dosage form of claim 10, wherein the weight ratio of COX-II inhibitor to muscle relaxant varies from 12.5:2.2 to 50:8.

40) (Amended) A pharmaceutical composition comprising:

a) a COX-II inhibitor selected from the group consisting of rofecoxib, celecoxib, flosulide, NS-398, DUP-697, meloxicam, 6-methoxy-2-naphthylacetic acid, nabumetone, etodolac, nimesulide, SC-~~5766, SC-58215~~ 57666, T-614, and combinations thereof;

b) a muscle relaxant selected from the group consisting of alcuronium, alosetron, aminophylline, baclofen, carisoprodol, chlorphenesin, chlorphenesin carbamate, chlorzoxazone, chlormezanone, cyclobenzaprine, dantrolene, decamethonium, diazepam, dyphylline, eperisione, ethaverine, gallamine triethiodide, hexafluorenium, mephenesin, metaxalone, methocarbamol, metocurine iodide, orphenadrine, pancuronium, papaverine, pipecuronium, pridinol, succinylcholine, theophylline, tizanidine, tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide and combinations thereof; and

c) at least one pharmaceutical excipient.

41) The composition of claim 40, wherein the at least one pharmaceutical excipient is independently selected from the group consisting of an acidifying agent, adsorbent,